I. SCIENTIFIC ABSTRACT

Gene Therapy for Malignant Mesothelioma

Malignant mesothelioma is a primary neoplasm of the mesothelial lining of the pleural or peritoneal cavity and accounts for approximately 6000 deaths per year. Although virtually all patients die within two years of diagnosis, malignant mesothelioma has a number of number of characteristics that make it an attractive model to study the feasibility of using gene therapy for localized malignancy. First, no effective therapy currently exists. Second, the location in the potential space of the thoracic cavity, makes the tumor is uniquely accessible, facilitating directed administration of therapeutic agents and subsequent analysis of treatment effects. Third, local extension of disease, rather than the development of widespread distant metastases, is responsible for the majority of the morbidity and mortality associated with this neoplasm.

We propose in this protocol, a Phase I trial to assess the safety and feasibility of treating patients with malignant mesothelioma by direct delivery of an adenovirus containing the Herpes Simplex thymidine kinase gene (HSV*TK*) into the pleural space, followed by systemic treatment with the antiviral drug ganciclovir (GCV). The rationale for this human protocol was based on previous successful experiments using the HSV*TK*/GCV system transferred via retroviral vectors to treat brain tumors and our own preclinical studies in animal models that demonstrated the efficacy of the HSV*TK*/GCV system using an adenovirus vector in eradicating established human mesothelioma tumors growing within the peritoneal cavity of immunodeficient mice and pleural cavity of immunocompetent rats.

In the Phase I protocol, patients will be treated with HSV*TK*-expressing replication deficient adenovirus and followed for a) evidence of HSV*TK* gene transfer and expression, b) immunological responses to HSV*TK* or adenoviral proteins, and c) toxicity. Adult patients with advanced malignant mesothelioma who are considered acceptable candidates for two thorocoscopic procedures will be considered. After thoroscopic confirmation of diagnosis, a suspension of virus will be delivered into the pleural space via a chest tube. Tumor biopsies will be harvested for analyses by follow-up thoracoscopy 3 days after instillation of virus. At that time, GCV will administered by intravenous infusion for 14 days. Patients will subsequently be carefully evaluated using clinical, laboratory, and radiographic analyses.

These studies will provide the scientific and clinical foundation for a future Phase II clinical trial for the treatment of mesothelioma. In addition, information will be obtained that will be useful for the planning of additional clinical trials focused on the treatment of other localized malignancies such as brain tumors, ovarian and bladder carcinomas, and metastatic disease to the meninges.